with diethyl ether to give 3(S)-N-hydroxy-4-(4-(4-bromophenoxy)benzensulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide.

Anal. calc. for $C_{19}H_{21}N_2O_5S_2Br$: C, 45.51; H, 4.22; N, 5.59; S, 12.79; Br, 15.94;

Found: C, 45.31; H, 4.17; N, 5.50; S, 12.69; Br, 16.09.

The following compound can be prepared in a similar manner:

(b) 3(S)-N-hydroxy-2,2-dimethyl-4-(4-(4-fluorophenoxy)benzene-sulfonyl)-tetrahydro-2H-1,4-thiazine-3-carboxamide.

Example 17

(a) 1(R),3(S)-N-hydroxy-4-(4-(4-bromophenoxy)benzenesulfonyl)-2,2-dimethyl-1-oxo-tetrahydro-2H-1,4-thiazine-3-carboxamide

Step 1. A solution of t-butyl 3(S)-4-(4-(4-bromophenoxy)benzene-sulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylate (0.65 g, 1.2 mmol) in acetic acid (2 mL) was treated with $NaBO_3 \cdot 4H_2O$ (0.23 g, 1.5 mmol) and stirred at room temperature for 2 hours, after which the reaction mixture was diluted with ethyl acetate, washed with water and saturated sodium bicarbonate, dried over sodium sulfate and evaporated. The foamy residue was twice chromatographed on silica gel (20% hexane:ethyl acetate) to give t-butyl 1(R),3(S)-4-(4-(4-bromophenoxy)benzenesulfonyl)-2,2-dimethyl-1-oxo-tetrahydro-2H-1,4-thiazine-3-carboxylate as a white foam.

Anal. calc. for $C_{23}H_{28}NO_6S_2Br$: C, 49.46; H, 5.05; N, 2.51; S, 11.48; Br, 14.31;

Found: C, 49.44; H, 5.11; N, 2.53; S, 11.55; Br, 14.21.

Step 2. A solution of t-butyl 1(R),3(S)-4-(4-(4-bromophenoxy)benzenesulfonyl)-2,2-dimethyl-1-oxo-tetrahydro-2H-1,4-thiazine-3-carboxylate (0.37 g, 0.66 mmol) in dichloromethane (4 mL) and TFA (4 mL) was stirred at room temperature for 7 hours, after which the solvents were evaporated and the residue azeotroped from benzene. The product was triturated with a warm 50% diethyl ether:hexane solution and

filtered to give 1(R),3(S)-4-(4-(4-bromophenoxy)benzenesulfonyl)-2,2-dimethyl-1-oxo-tetrahydro-2H-1,4-thiazine-3-carboxylic acid as a white solid.

Anal. calc. for $C_{19}H_{20}NO_6S_2Br$: C, 45.42; H, 4.01; N, 2.79; S, 12.76; Br, 15.90;

Found: C, 45.51; H, 4.08; N, 2.84; S, 12.66; Br, 15.83

Step 3. A solution of 1(R),3(S)-4-(4-(4-bromophenoxy)benzenesulfony1-2,2-dimethyl-1-oxo-tetrahydro-2H-1,4-thiazine-3-carboxylic acid (0.32 g, 0.64 mmol) in dichloromethane (3 mL) and DMF (1 mL) was cooled to 0°C and treated with O-t-butyldimethylsilyl hydroxylamine (0.11 g, 0.76 mmol) immediately followed by EDC (0.183 g, 0.96 mmol). The resulting reaction mixture was stirred at 0°C for 80 minutes, after which additional O-t-butyldimethylsilyl hydroxylamine (0.094 g, 0.64 mmol) and EDC (0.15 g, 0.76 mmol) were added, and the mixture was stirred at 0°C for an additional hour and at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate and washed with 5% citric acid, water and saturated sodium bicarbonate, to give 1(R),3(S)-N-(t-butyldimethylsilyl)oxy-4-(4-(4-bromophenoxy) benzenesulfonyl)-2,2-dimethyl-1-oxo-tetrahydro-2H-1,4-thiazine-3-carboxamide, which was next used without further purification.

Step 4. A solution of 1(R),3(S)-N-(t-butyldimethylsilyl)oxy-4-(4-(4-bromophenoxy)benzenesulfonyl)-2,2-dimethyl-1-oxo-tetrahydro-2H-1,4-thiazine-3-carboxylic acid O-t-butyldimethylsilyl hydroxamide (0.13 g, 0.21 mmol) in dichloromethane (2 mL) and TFA (1 mL) was stirred at room temperature for 2 hours, after which the solvents were evaporated and the residue was azeotroped from benzene. The resulting white solid was filtered and washed with diethyl ether to give 1(R),3(S)-N-hydroxy-4-(4-(4-bromophenoxy)-benzenesulfonyl)-2,2-dimethyl-1-oxo-tetrahydro-2H-1,4-thiazine-3-carboxamide.

Anal. calc. for $C_{19}H_{21}N_2O_6S_2Br$: C, 44.10; H, 4.09; N, 5.41; S, 12.39;

Found: C, 43.84; H, 4.20; N, 5.37; S, 12.25.

The following compound can be prepared in a similar manner:

(b) 1(R),3(S)-N-hydroxy-1-oxo-2,2-dimethyl-4-(4-(4-fluorophenoxy) benzenesulfonyl)-tetrahydro-2H-1,4-thiazine-3-carboxamide.

Example 18

(a) 3(S)-N-hydroxy-4-(4-((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide

Step 1. To a stirred solution of D-penicillamine in 20 mL of dry DMF was added diisopropylethylamine (1.74 mL) followed by, in a dropwise manner, trimethylsilyl chloride (1.52 mL). After 30 minutes, diazabicyclo[4.2.0]undecane (4.48 mL) was added to the clear solution, and the resulting solution was slowly transferred via cannula over a 1 hour period to a solution of 1,2-dibromoethane (0.95 mL) in 20 mL of dry DMF at 50°C. After the addition was complete, the solution was heated for an additional 1 hour at 50°C, and then cooled to 0°C. To the stirred solution was added N-methylmorpholine (1.00 mL), followed by 9-fluorenylmethoxycarbonyl chloride (2.84 g), and the solution was kept at -20°C for 16 hours. An additional 0.50 g of 9-fluorenylmethoxycarbonyl chloride was added, and the solution was stirred for an additional 1 hour at 0°C and then quenched with 1 mL of water. The reaction was partitioned between 3:1 ethyl acetate:hexane (200 mL) and 0.2 N aqueous sodium bisulfate (200 mL). The organic layer was washed with additional 0.2 N aqueous sodium bisulfate solution (150 mL) and with brine (50 mL), dried over sodium sulfate and concentrated. The residue was purified by chromatography on 150 g of silica gel, eluting with 25% to 35% ethyl acetate:hexane containing 0.5% acetic acid. The product-containing fractions were concentrated to give a syrup, which was twice concentrated from toluene, and finally from t-butyl methyl ether:isooctane, to give 2.84 g of 3(S)-4-(9-fluorenylmethoxy-carbonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid as a white solid.

Step 2. To a solution of 3(S)-4-(9-fluorenylmethoxycarbonyl)-2,2- dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid (2.98 g) in 20 mL of dichloromethane at 0°C was added O-(t-butyldiphenyl- silyl)hydroxylamine (2.71 g) followed by EDC hydrochloride (1.58 g). The reaction was stirred at

0°C to 25°C for 16 hours and then partitioned between 1:1 ethyl acetate:hexane (200 mL) and 0.2 N pH 7 phosphate buffer (100 mL). The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on 150 g of silica gel, eluting with 20% to 30% ethyl acetate:hexane, to provide, after concentration from dichloromethane:isooctane, 3(S)-N-(t-butyldiphenylsilyl)oxy-4-(9-fluorenylmethoxycarbonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide (4.42 g) as a white solid.

Step 3. To a solution of 3(S)-N-(t-butyldiphenylsilyl)oxy-4-(9-fluorenylmethoxycarbonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide (4.33 g) in THF (10 mL) was added diethylamine (5 mL). After 1 hour, the solution was concentrated and the residue was chromatographed on 75 g of silica gel, eluting with ethyl acetate, to give 3(S)-N-(t-butyldiphenylsilyl) oxy-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide (2.11 g) as a sticky solid foam.

Step 4. To a solution of 4-phenoxypyridine (6.84 g) in 20 mL of 1,2-dichloroethane at 0°C was added 8.0 mL of chlorosulfonic acid in a dropwise manner. After 10 minutes, the ice bath was removed and the solution was allowed to warm to 25°C. After an additional 1 hour, the solution was heated to 40°C for 3 hours, and then cooled to 25°C, and oxalyl chloride (4.4 mL) was added. The solution was heated to 50°C for 16 hours, and then an additional 2.2 mL of oxalyl chloride was added. After 5 hours more at 5°C, the solution was cooled to 25°C, and poured with rapid stirring into 250 mL of diethyl ether. After 1 minute, the solids were allowed to settle and the supernatant was decanted. The residue was suspended in 3:1 toluene:dichloromethane (250 mL) at about 5°C and 50 mL of 1.6 M aqueous K_3PO_4 was added with stirring. After about 30 seconds, the mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with 25 mL of 1 N pH 7 phosphate buffer and with 10 mL of brine, and the combined aqueous layers were extracted with 50 mL of toluene. The combined organic layers were dried over sodium sulfate then

filtered through a glass-fiber filter. To the filtrate was immediately added 11 mL of 4 M HCl in dioxane and the solution was then concentrated. Partial concentration from dichloromethane:t-butyl methyl ether and filtration gave 2.11 g of 4-((pyrid-4-yl)oxy)benzenesulfonyl chloride hydrochloride.

Step 5. To a solution of 3(S)-N-(t-butyldiphenylsilyl)oxy-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide (2.11 g) in dichloromethane (20 mL) at 0-C was added N-methylmorpholine (1.35 mL) followed by 4-((pyrid-4-yl)oxy)benzenesulfonyl chloride hydrochloride (1.71 g). The solution was stirred at 0°C for 3 hours, and then at 25°C for 4 hours. The reaction was partitioned between 3:1 ethyl acetate:hexane (150 mL) and 0.5 N pH 7 phosphate buffer (50 mL). The organic layer was washed with additional buffer and with brine, dried over sodium sulfate and concentrated. The residue was chromatographed on 150 g of silica gel, eluting with 30% to 50% ethyl acetate:dichloromethane to give, after partial concentration from dichloromethane:isooctane, 3(S)-N-(t-butyldiphenylsilyl)oxy-4-(4-((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide (2.36 g) as a pale yellow solid.

Step 6. To a solution of 3(S)-N-(t-butyldiphenylsilyl)oxy-4-(4- ((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1, 4-thiazine-3-carboxamide (2.25 g) in methanol (10 mL) was added 5 mL of a 10% solution of concentrated HCl in methanol. After 1 hour at 25°C, the solution was diluted with methanol (50 mL) and treated with Amberlite IRA-68 weakly basic resin (about 15 mL) until the pH measured 7.2. The resin was removed by filtration and washed well with methanol, and then the filtrate was concentrated to about 10 mL. Addition of 20 mL of t-butyl methyl ether gave a voluminous precipitate, which was collected by filtration to give 1.19 g of an off-white solid. The solid was dissolved in 50 mL of 10% methanol in ethyl acetate and filtered through a 0.45 µm syringe filter to remove trace particles. The filtrate was partially concentrated to about 20 mL, diluted with additional ethyl acetate and reconcentrated to about 20 mL. The crystalline precipitate was collected by filtration and dried *in vacuo* to give 3(S)-N-hydroxy-4-(4-

((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide (0.97 g) as a white solid: mp 149.8°C.

Anal. calc. for $C_{18}H_{21}N_3O_5S_2.0.5\ H_2O$: C, 49.47; H, 5.19; N, 9.62; S, 14.67;

Found: C, 49.49; H, 5.15; N, 9.37; S, 14.41.

The following compound was prepared in a similar manner:

(b) 3(S)-N-hydroxy-4-(4-((pyrid-2-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide;

HRMS (FAB) calc. for $(M+Cs)^+$: 556.9977; found: 556.9963.

Anal. calc. for $C_{18}H_{21}N_3O_5S2 \cdot 0.75\ H_2O$: C, 49.47; H, 5.19; N, 9.62; S, 14.67;

Found: C, 49.22; H, 4.81; N, 9.57; S, 14.69;

The following compound can be prepared in a similar manner:

(c) 3(S)-N-hydroxy-4-(4-(4-(imidazol-2-yl)phenoxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide.

Example 19

(a) 1(S), 3(S)-N-hydroxy-4-(4-((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-1-oxotetrahydro-2H-1,4-thiazine-3-carboxamide and 1(R), 3(S)-N-hydroxy-4-(4-((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-1-oxotetrahydro-2H-1,4-thiazine-3-carboxamide

To a solution of 3(S)-N-hydroxy-4-(4-((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide (0.423 g, 1.00 mmol) in 30 mL of 5:1 dichloromethane:methanol at -10°C was added 0.15 g (0.85 mmol) of m-chloroperbenzoic acid in portions over a 2 hour period. The solution was diluted with 60 mL of methanol and then passed through 10 mL of Amberlite IRA-68 weakly basic resin to remove the byproduct m-chlorobenzoic acid. The filtrate was concentrated and the residue was chromatographed with 6% to 12% methanol in dichloromethane. Eluting first was 1(S), 3(S)-N-hydroxy-4-(4-((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-1-oxotetrahydro-2H-1,4-thiazine-3-carboxamide (200 mg): ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.92 (s, 1H), 9.04 (s, 1H), 8.57 (m, 2H), 7.90 (d, J = 8.5

Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 4.5 Hz, 2H), 4.39 (s, 1H), 4.33-4.20 (m, 1H), 3.94-3.86 (m, 1H), 3.21-3.10 (m, 1H), 3.02 (d, J = 15 Hz, 1H), 1.42 (s, 3H), 1.25 (s, 3H);

Anal. calc. for $C_{18}H_{21}N_3O_6S_2 \cdot 0.15H_2O$, 0.1EtOAc: C, 49.00; H, 4.94; N, 9.32; S, 14.22. Found : C, 48.99; H, 4.97; N, 9.27; S, 14.32.

Continued elution provided 1(R), 3(S)-N-hydroxy-4-(4-((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-1-oxotetrahydro-2H-1,4-thiazine-3-carboxamide (50 mg): ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.98 (s, 1H), 9.20 (s, 1H), 8.58 (d, J = 6 Hz, 2H), 7.89 (d, J = 9 Hz, 2H), 7.40 (d, J = 9 Hz, 2H), 7.12 (d, J = 6 Hz, 2H), 4.40 (s, 1H), 4.10-3.90 (m, 2H), 3.45-3.35 (m, 1H), 2.70-2.50 (m, 1H), 1.27 (s,3H), 1.25 (s, 3H); LSIMS: m/e expected for $C_{18}H_{21}N_3O_6S_2+H^+$ = 440; m/e observed = 440.

Anal. calc. for $C_{18}H_{21}N_3O_6S_2 \cdot 0.2H_2O$, 0.3EtOAc: C, 49.11; H, 5.11; N, 8.95; S, 13.66. Found : C, 49.21; H, 4.98; N, 8.99; S, 13.60.

The following compound was prepared in a similar manner:

(b) 1(R), 3(S)-N-hydroxy-4-(4-(4-chlorophenoxy)benzenesulfonyl)-2,2-dimethyl-1-oxo-tetrahydro-2H-1,4-thiazine-3-carboxamide.

mp 145-147 °C. Anal. Calcd for $C_{19}H_{21}ClN_2O_6S_2$*0.8H2O: C, 48.3; H, 4.48; N, 5.93; S, 13.55; Cl, 7.41. Found: C, 46.96; H, 4.69; N, 5.64; S, 13.01; Cl, 7.30.

Example 20

3(S)-4-(4-(4-(furan-3-yl)phenoxy)benzenesulfonyl-N-hydroxy-tetrahydro-2H-1,4-thiazine-3-carboxamide

Step 1. To a suspension of D-penicillamine (0.75 g, 5 mmol) in 10 mL of dry DMF was added 0.87 mL (5 mmol) of diisopropylethylamine, followed by 0.75 mL (6 mmol) of trimethylsilyl chloride. After twenty minutes, 1,8-diazabicyclo [5.4.0]undec-7-ene (2.24 mL, 15 mmol) was added to the homogeneous solution and the solution was transferred to an addition funnel and then added dropwise over a 1 hour period to a stirred solution of 0.50 mL

(5.8 mmol) of 1,2-dibromoethane in 10 mL of DMF at 50 °C. After an additional 30 minutes after the addition was complete, the solution was cooled to 0 °C, and 0.55 mL (5 mmol) of N-methylmorpholine was added, followed by the dropwise addition of a solution of 4-(4-bromophenoxy)benzenesulfonyl chloride (1.94 g, 5.5 mmol) in 5 mL of DMF over a 15 minute period. The reaction was stirred for 2 hours at 0 °C and then allowed to warm to room temperature. After an additional 2 hours, 0.3 g more of 4-(4-bromophenoxy)benzenesulfonyl chloride was added. After an additional 15 minutes, the reaction was partitioned between 0.2 N aq. sodium bisulfate and 1:1 ethyl acetate:hexane. The aqueous layer was extracted twice with 1:1 ethyl acetate:hexane, and the combined organic layers were washed with 0.2 N aq. sodium bisulfate and with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel, eluting with a gradient from dichloromethane to 8% methanol in dichloromethane, to provide, after rotary evaporation from dichloromethane/t-butyl methyl ether, 3(S)-4-(4-(4-bromophenoxy)benzenesulfonyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid (0.84 g, 37%) as a solid foam: ^{1}H NMR ($CDCl_3$): δ 7.70 (d, 2H, J=9.19 Hz), 7.50 (d, 2H, J=8.82 Hz), 7.01 (d, 2H, J=8.83 Hz), 6.94 (d, 2H, J=8.82 Hz), 4.50 (s, 1H), 4.01 (d, 1H, J=13.24 Hz), 3.7-3.6 (m, 1H), 3.2-3.1 (m ,1H), 2.42 (d, 1H, J=13.98 Hz), 1.61 (s, 3H), 1.39 (s, 3H)

Step 2. A mixture of 0.45 g (1.0 mmol) of 3(S)-4-(4-(4-bromophenoxy) benzenesulfonyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid and 0.11 g (1.0 mmol) of 3-furan boronic acid (*J. Org. Chem.* **1984,** *49*, 5237-5243) in 2 mL of benzene, 2 mL of 2M aq. sodium carbonate, and 1.5 mL of ethanol was deoxygenated with a stream of argon for 15 minutes, and then 115 mg (0.1 mmol) of tetrakis(triphenylphosphine)palladiumwas added and the mixture was heated at 80 °C for six days. After cooling to room temperature, the mixture was partitioned between ethyl acetate and pH 4 citrate buffer. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were washed with brine, dried over sodium sulfate, and

concentrated. The residue was purified by chromatography on silica gel, eluting with a gradient from dichloromethane to 5% methanol in dichloromethane, to provide 3(S)-4-(4-(4-(furan-3-yl)phenoxy)benzenesulfonyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid (0.317 g, 67%) as a sticky solid foam. FAB$^+$MS Calcd for M+Cs$^+$=606.0021. Obs 606.0036; ^{1}H NMR ($CDCl_3$) δ 7.72-7.43 (m, 6H), 7.04 (d, 2H, J=8.46 Hz), 7.00 (d, 2H, J=8.82 Hz), 6.67 (s, 1H), 4.51 (s, 1H), 4.1-3.9 (bm, 1H), 3.7-3.6 (bm, 1H), 3.2-3.1 (bm, 1H), 2.42 (bd, 1H, J=12.87 Hz), 1.61 (s, 3H), 1.38 (s, 3H)

Step 3. To a solution of 3(S)-4-(4-(4-(furan-3-yl)phenoxy)benzenesulfonyl-tetrahydro-2H-1,4-thiazine-3-carboxylic acid (293 mg, 0.62 mmol) and O-(tert-butyldiphenylsilyl)hydroxylamine (0.22 g, 0.8 mmol) in 5 mL of dichloromethane was added EDC (132 mg, 0.69 mmol). After 18 hours at 25 °C, the mixture was partitioned between 1 N aq. sodium bisulfate and dichloromethane. The aqueous layer was extracted twice with dichloromethane, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel, eluting with a gradient from dichloromethane to 5% methanol in dichloromethane, to provide 3(S)-N-(tert-butyldiphenylsilyl)oxy-4-(4-(4-(furan-3-yl)phenoxy)benzenesulfonyl-tetrahydro-2H-1,4-thiazine-3-carboxamide (40 mg, 8%). FAB$^+$MS Calcd for M+Cs$^+$=859.1308 Obs 859.1274; ^{1}HNMR (d_6-DMSO): δ 10.81 (s, 1H), 8.17 (s, 1H), 7.74 (s, 1H), 7.67-7.61 (m, 8H), 7.45-7.30 (m, 6H), 7.10 (d, 2H, J=8.83 Hz), 7.00 (d, 2H, J=8.46 Hz), 6.94 (s, 1H), 4.06 (s, 1H), 3.95-3.89 (bm, 1H), 3.77-3.73 (bm, 1H), 2.87-2.78 (bm, 1H), 1.28 (s, 3H), 0.99 (s, 9H), 0.61 (s, 3H)

Step 4. To a 25 °C solution of 3(S)-N-(tert-butyldiphenylsilyl)oxy-4-(4-(4-(furan-3-yl)phenoxy)benzenesulfonyl-tetrahydro-2H-1,4-thiazine-3-carboxamide (35 mg) in 2 mL of THF was added 0.060 mL of 2M tetrabutylammonium fluoride in THF. After 30 minutes, the solution was partitioned between 1 M pH 7 phosphate buffer and ethyl acetate. The

aqueous layer was extracted once with ethyl aceate, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. The residue was triturated with hexane and the resulting solid was collected by filtration to yield 3(S)-4-(4-(4-(furan-3-yl)phenoxy)benzenesulfonyl-N-hydroxy-tetrahydro-2H-1,4-thiazine-3-carboxamide (22 mg). ^{1}H NMR ($CDCl_3$): δ 9.69 (bs, 1H), 7.24 (d, 2H, J=8.82 Hz), 7.51 (d, 2H, J=8.46 Hz), 7.05 (t, 4H, J=9.37 Hz), 6.69 (s, 1H), 4.57 (s, 1H), 4.02 (d, 1H, J=12.5 Hz), 3.28-3.12 (m, 2H), 2.50 (d, 1H, J=12.87 Hz), 1.61 (s, 3H), 1.31 (s, 3H).

Example 21

Step 1. To a stirred mixture of 2(R/S)-(tert-butoxycarbonyl)amino-3,3-dimethyl-4-pentenoic acid (3.6 g, 15 mmol) and anhydrous sodium bicarbonate (3.78 g, 45 mmol) in 25 mL of DMF was added methyl iodide (1.03 mL, 17 mmol) dropwise. The mixture was stirred for 27 hours at room temperature, and then poured into water (100 mL). The mixture was extracted with 2:1 ethyl acetate:hexane (3 x 50 mL), and the combined organic layers were washed with 5% aq. sodium thiosulfate solution, water, sat. aq. sodium bicarbonate, and finally with brine. The organic layer was dried over magnesium sulfate, and concentrated to provide methyl 2(R/S)-(tert-butoxycarbonyl)amino-3,3-dimethyl-4-pentenoate (3.37 g, 87%) as a syrup which was used without further purification.

Step 2. To a solution of methyl 2(R/S)-(tert-butoxycarbonyl)amino-3,3-dimethyl-4-pentenoate (4.97 g, 19.3 mmol) in 50 mL of dichloromethane at 0 °C was added 16.5 mL of trifluoroacetic acid. After 2 hours, the solution was concentrated and the residue was dissolved in 100 mL of dichloromethane and washed with sat. aq. sodium bicarbonate (50 mL). The organic layer was dried over sodium sulfate and concentrated to give methyl 2(R/S)-amino-3,3-dimethyl-4-pentenoate (2.30 g), which was dissolved in 50 mL of dichloromethane and cooled to 0 °C. Triethylamine (8.1 mL, 58 mmol) was added, followed by addition of 4-(4-fluorophenoxy)benzenesulfonyl chloride

(6.71 g, 21.3 mmol). The reaction was allowed to warm to room temperature and stirred for 18 hours and then washed 3 N hydrochloric acid (125 mL), dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel, eluting with 20% ethyl acetate in hexane, to yield 4.41 g (61%) of methyl 2(R/S)-[4-(4-fluorophenoxy)benzenesulfonyl]amino-3,3-dimethyl-4-pentenoate as a white solid.

Anal. Calcd for $C_{20}H_{22}FNO_5S$: C, 58.96; H, 5.44; N, 3.44; S, 7.87. Found: C, 59.01; H, 5.47; N, 3.50; S, 7.95.

Step 3. A mixture of methyl 2(R/S)-[4-(4-fluorophenoxy)benzenesulfonyl]amino-3,3-dimethyl-4-pentenoate (4.31 g, 10.6 mmol) and potassium carbonate (3.65 g, 26.4 mmol) was stirred vigorously in 25 mL of DMF at 65 °C as ethyl bromoacetate was added dropwise. After 16 hours, an additional 1.82 g of potassium carbonate and 4.1 mL of ethyl bromoaceate was added. After an additional 3 hours at 65 °C, 6.0 mL of ethyl bromoaceate was added and stirring was continued for another 4 hours. After cooling to room temperature, the solvent was removed *in vacuo* (~ 1 torr), and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water and with brine, dried over sodium sulfate, and concentrated. The residue was chromatographed on silica, eluting with a gradient of 10% to 20% ethyl acetate in heaxane to provide 4.05 g (78%) of methyl 2(R/S)-[4-(4-fluorophenoxy) benzenesulfonyl][(ethoxycarbonyl)methyl]amino-3,3-dimethyl-4-pentenoate.

Anal. Calcd for $C_{24}H_{28}FNO_7S$: C, 58.42; H, 5.72; N, 2.84; S, 6.50. Found: C, 58.34; H, 5.75; N, 2.90; S, 6.40.

Step 4. To a mixture of methyl 2(R/S)-[4-(4-fluorophenoxy)benzenesulfonyl] [(ethoxycarbonyl)methyl]amino-3,3-dimethyl-4-pentenoate (3.52 g, 7.13 mmol) in 40 mL of 2:2:3 carbon tetrachloride:acetonitrile:water was added 0.037 g (0.18 mmol) of ruthenium trichloride monohydrate and 7.78 g (36.4 mmol) of sodium periodate. The mixture was stirred vigorously at room temprature for 22 hours, then diluted with 150 mL of water and extracted with

dichloromethane (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel, eluting with a gradient from 1:1 ethyl acetate:hexane to ethyl acetate, to yield 2(R/S)-[4-(4-fluorophenoxy) benzenesulfonyl][(ethoxycarbonyl)methyl]amino-3,3-dimethyl-butanedioic acid, 1-methyl ester (2.27 g, 62%) as an off-white solid.

Step 5. To a solution of methyl 2(R/S)-[4-(4-fluorophenoxy)benzenesulfonyl] [(ethoxycarbonyl)methyl]amino-3,3-dimethyl-butanedioic acid (2.00 g, 3.91 mmol) and triethylamine (0.6 mL, 4.30 mmol) in 50 mL of benzene at 80 °C was added diphenyylphosphoryl azide (0.93 mL, 4.3 mmol). After 4 hours, benzyl alcohol (1.62 mL, 15.6 mmol) was added. After an additional 20 hours, the reaction was cooled to room temperature and partitioned between ethyl acetate and 10% aq. citric acid. The organic layer was washed with sat. aq. sodium bicarbonate, dried over sodium sulfate, and concentrated. The excess benzyl alcohol was removed by kugelrohr distillation at 0.28 torr, 70 °C, and the residue was purified by chromatography on silica, eluting with 30% ethyl acetate in hexane, to give methyl 2(R/S)-[4-(4-fluorophenoxy)benzenesulfonyl][(ethoxycarbonyl)methyl]amino-3-(benzyloxycarbonyl)amino-3-methylbutanoate (1.81 g, 75%) as a colorless, viscous oil.

Anal. Calcd for $C_{29}H_{33}FN_2O_9S$: C, 58.34; H, 5.55; N, 4.54; S, 5.19. Found: C, 58.50; H, 5.43; N, 4.60; S, 5.16.

Step 7. A solution of methyl 2(R/S)-[4-(4-fluorophenoxy)benzenesulfonyl] [(ethoxycarbonyl)methyl]amino-3-(benzyloxycarbonyl)amino-3-methylbutanoate (1.89 g, 3.06 mmol) in 50 mL of ethanol was hydrogenated over 0.19 g of 10% palladium on carbon under 1 atm of hydrogen for 1 hour at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was triturated with 50 mL of warm diethyl ether and filtered to give 1.07 g (80%) of methyl 2(R/S)-1-[4-(4-

fluorophenoxy)benzenesulfonyl]-3,3-dimethyl-5-oxo-piperazine-2-carboxylate as an off-white solid.

Anal. Calcd for $C_{20}H_{21}FN_2O_6S$: C, 55.04; H, 4.85; N, 6.42; S, 7.35. Found: C, 55.15; H, 4.95; N, 6.33; S, 7.20.

Step 8. A solution of methyl 2(R/S)-1-[4-(4-fluorophenoxy)benzenesulfonyl]-3,3-dimethyl-5-oxo-piperazine-2-carboxylate (0.20 g, 0.46 mmol) and 0.123 g (0.92 mmol) of lithium iodide in 8.8 mL of freshly-distilled 2,6-lutidine was heated at 120 °C. After 1.25 hours at 120 °C, an additional 0.123 g of lithium iodide was added. After an additional 3 hours, more lithium iodide (0.123 g) was added and the reaction was stirred for another 2 hours. After cooling to room temperature, the reaction was poured into water (75 mL) and extracted with 3 x 40 mL of ethyl acetate (to remove 2,6-lutidine). The aqueous layer was then acidified and extracte with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate, treated with decolorizing carbon, filtered, and concentrated. The oily residue was triturated with diethyl ether (5 mL) and hexane (2 mL). The solid was collected by filtration and washed with diethyl ether to provide 121 mg (62%) of 2(R/S)-1-[4-(4-fluorophenoxy)benzenesulfonyl]-3,3-dimethyl-5-oxo-piperazine-2-carboxylic acid as a beige solid.

Anal. Calcd for $C_{19}H_{19}FN_2O_6S$: C, 54.02; H, 4.53; N, 6.63; S, 7.59. Found: C, 54.13; H, 4.59; N, 6.54; S, 7.47.

Step 9. To a stirred solution of 2(R/S)-1-[4-(4-fluorophenoxy)benzenesulfonyl]-3,3-dimethyl-5-oxo-piperazine-2-carboxylic acid (50 mg, 0.12 mmol) and N-methyl morpholine (0.10 mL) in DMF (0.5 mL) at 25 °C was added 92 mg (0.18 g) of PyBOP followed by addition of 33 mg (.47 mmol) of hydroxylamine hydrochloride. After 22.5 hours , the reaction was partitioned between ethyl acetate and 10% aqueous citric acid, and the organic layer was washed with water, sat. aq. sodium bicarbonate, water, and brine. The organic layer was dried over sodium sulfate and concentrated, and the residue was redissolved in 20 mL of diethyl ether and partially concentrated to provide 0.23 g of a white solid which was somewhat impure

accoring to TLC analysis. Purification by chromatography on silica, eluting with 0.5% acetic acid in ethyl acetate, provided 7.1 mg of 2(R/S)-1-[4-(4-fluorophenoxy)benzenesulfonyl]-3,3-dimethyl-N-hydroxy-5-oxo-piperazine-2-carboxamide: FAB HRMS calcd. for $C_{19}H_{21}FN_3O_6S$ $(M+H)^+$: 438.1135. Found: 438.1145.

Anal. Cal. for $C_{19}H_{20}N_3O_6SF \cdot 0.25H_2O$: C, 51.63; H, 4.68; N, 9.51; S, 7.26. Found: C, 51.58; H, 4.70; N, 9.42; S, 7.1.7.

Example 22

2(R/S)-3-acetyl-1-4-(4-fluorophenoxy)benzenesulfonyl-N-hydroxy-hexahydropyrimidine-2-carboxamide

Step 1. To a stirred solution of 1,3-diaminopropane (6.7 mL) in 100 mL of dichloromethane at -10 °C was slowly added over a 2 hour period a solution of 4-(4-fluorophenoxy)benzenesulfonyl chloride (5.7 g, 20 mmol) in 50 mL of dichloromethane. The reaction was stirred for 15 minutes after the addition was complete, and then partitioned between ethyl acetate and water. The resulting emulsion was cleared by addition of dichloromethane, and the organic layer was separated. The aqueous layer was extracted with dichloromethane and the combined organic layers were extracted with 0.5 N aq. sodium bisulfate. The aqueous phase was brought to pH 8 with sodium bicarbonate and then extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over sodium sulfate and concentrated to a volume of about 50 mL. Addition of hexane resulting in formation of a precipitate, which was collected by filtration to provide N-(3-aminopropyl)-4-(4-fluorophenoxy)benzenesulfonamide (4.27 g) as a white solid: mp 184 °C (softens), 237 °C (melts) ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.84 (d, J = 9 Hz, 2H), 7.38-7.21 (m, 4H), 7.12 (d, J = 9 Hz, 2H), 3.6-3.2 (br s, 3H), 2.80 (dd, J = 7, 7 Hz, 2H), 2.77 (dd, J = 7, 7 Hz, 2H), 1.72-1.60 (m, 2H).

Step 2. To a solution of N-(3-aminopropyl)-4-(4-fluorophenoxy) benzenesulfonamide (3.24 g, 10 mmol) in 100 mL of dichloromethane was added 2.26 mL of a 50% solution of ethyl glyoxalate in toluene. After 2 hours,

10 g of 3 A molecular sieves were added. After 18 hours, an additonal 2.26 mL of ethyl glyoxalate was added portionwise while monitoring the reaction progress by TLC. After 4 hours, the reaction was filtered through Celite 545, and the filtrate was concentrated. The residue was purified by chromatography on silica, eluting first with 2:2:1 hexane:dichloromethane:ethyl acetate and then with 1:3 ethyl acetate:dichloromethane, to give 1.2 g of a mixture of two compounds by TLC analysis, which was employed without further purification in the next reaction.

Step 3. To a solution of the product (1.1 g) from the previous paragraph in 25 mL of dichloromethane was added 0.67 mL of 4 M hydrogen chloride in dioxane. After 1 hour at room temperature, the solution was cooled to -20 °C, and acetyl chloride (0.19 mL) was added, followed by addition of N-methyl morpholine (0.89 mL). After 2 hours at -20 °C and 1.5 hours at room temprature, the reaction was partitioned between water and ethyl acetate. The organic layer was dried over sodium sulfate, concentrated, and the residue was purified by chromatography, eluting with 40% acetone in hexane, to yield ethyl 2(R/S)-3-acetyl-1-4-(4-fluorophenoxy)benzenesulfonyl-hexahydropyrimidine-2-carboxylate (0.24 g) as a clear syrup: LSI MS m/e expected for $C_{21}H_{24}FN_2O_6S$ $(M+H)^+$: 451. Found: 451.

Step 4. A solution of ethyl 2(R/S)-3-acetyl-1-4-(4-fluorophenoxy)benzenesulfonyl-hexahydropyrimidine-2-carboxylate (0.225 g) and hydroxylamine (0.10 mL of a 50% aqueous solution) in 5 mL of ethanol was stirred at 25 °C for 18 hours, and then at 55 °C for 24 hours. The reaction solution was concentrated and chromatographed, eluting first with 40% ethyl acetate in dichloromethane and then with 54:40:5:1 dichloromethane:ethyl acetate:methanol:acetic acid, to yield 37 mg (17%) of 2(R/S)-3-acetyl-1-4-(4-fluorophenoxy)benzenesulfonyl-N-hydroxy-hexahydropyrimidine-2-carboxamide as a white foam after concentration from dichloromethane/isooctane: mp 79°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.0 (br s, 1H), 9.05 (br s, 1H), 7.79 (d, J = 9 Hz, 2H), 7.39-7.30 (m, 2H), 7.28-7.21 (m, 2H), 7.12 (d, J = 9 Hz, 2H), 6.77 (s, 1H), 3.73 (d, J = 14.5 Hz, 1H), 3.58

(d, J = 13 Hz, 1H), 3.33-3.13 (m, 2H), 1.93 (s, 3H), 1.44-1.35 (m, 1H), 1.17-1.07 (m, 1H); HRMS (FAB) (+Cs)+expected: 570.0111. Found 570.0122.

Anal. calc. for $C_{19}H_{20}FN_3O_6S \cdot 0.1\ CH_2Cl_2 \cdot 0.25$ isooctane: C, 52.05; H, 4.97; N, 9.06; S, 6.91. found: C, 52.03; H, 5.00; N, 9.05; S, 6.85.

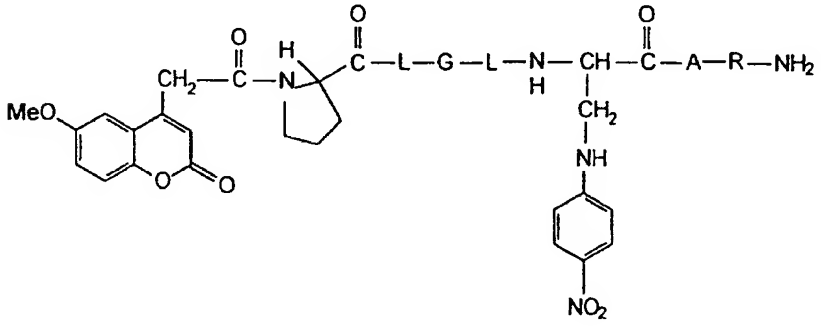
Anal. calc. for $C_{21}H_{23}N_2O_6SF/* \cdot 0.4H_2O$, 0.3 hexane, 0.1 toluene: C, 52.72; H, 5.01; N, 9.09;, S, 6.93. Found: C, 52.75; H, 4.96; N, 9.03; S, 6.78.

The results obtained during biological testing of some preferred embodiments of the inventive compounds are described below.

BIOLOGICAL DATA

Enzyme Assays

Stromelysin enzymatic activity was measured using a modified version of a resonance energy transfer fluorogenic assay as desribed in *FEBS*, vol. 296(3), p. 263 (1992), the disclosure of which is incorporated herein by reference. The MCA-peptide substrate is shown below. The fluorescent MCA group is quenched by resonance energy transfer to the 2,4-dinitrophenyl group. Matrix metalloproteinases cleave this substrate at the Gly-Leu bond. Cleavage results in the loss of energy transfer and a large increase in fluorescence of the MCA group.



7-methoxycoumarin-4-yl-acetyl-pro-leu-gly-leu-3-(2,4-dinitrophenyl)-L-2,3-diaminoproprionyl-ala-arg-NH_2

The MCA assay was performed at 37°C in buffer containing 50 mM Tricine (pH 7.5), 10 mM $CaCl_2$, 200 mM NaCl, and 1% DMSO with the

following concentrations of matrix metalloproteinases: 1.4 nM stromelyin, 0.063 nM matrilysin, and 0.030 nM gelatinase A. The concentration of MCA substrate was 10 or 20 μM in a final volume of 1.6 mL. Fluorescence data was collected with Perkin-Elmer LS-5B and LS-5B spectrofluorimeters with $\lambda_{excitation}$ = 328 nm and $\lambda_{emission}$ = 393 nm. Spectrofluorimeters were interfaced with IBM-compatible microcomputer systems.

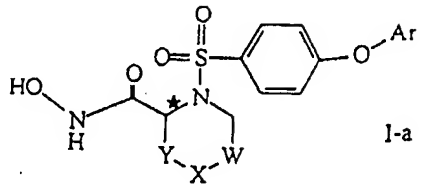
Competitive Inhibition Analyses

The K_m for the MCA peptide substrate with the matrix metalloproteinases is quite high and exceeds its solubility under assay conditions. Consequently, the apparent K_i ($K_{i,app}$) was determined to describe the strength of inhibition. However, in this case, $K_{i,app}$ would be essentially equal to K_i since $[S] \ll K_m$. For the determination of $K_{i,app}$, the concentration of the inhibitor was varied at a constant and low concentration of substrate and the steady-state rates of fluorescence change determined. In most cases absorptive quench due to the presence of ligand was not observed. For slow-binding inhibitors, onset of inhibition curves were collected for at least 45 minutes so that equilibrium was established. Steady-state rates of fluorescence change were obtained by fitting a curve to an equation for a single exponential decay containing a linear phase. The fitted value of the linear phase was taken as the steady-state rate. The steady-state rates were fitted to the Michaelis equation describing competitive inhibition by non-linear methods. Data resulting from tight-binding inhibition was analyzed, and $K_{i,app}$ determined by fitting the data to the tight-binding equation of Morrison See (*Biochem. Biophys. Acta*, vol. 185, pp. 269-286 (1969)) by non-linear methods.

The results of the above-described tests are presented below in Table 1.

TABLE 1

Enzyme Inhibition Constants (K_i) nM



I-a

Variable						Enzyme				
*	W	X	Y	Z	Ar	HSLN	Matr.	HFC	HG72kD	Coll3
R/S	CH_2	N-$CO_2C(CH_3)_3$	CH_2	O	4-bromophenyl	0.730	378.00	60.00	0.025	0.070
R/S	CH_2	N-H (HCl salt)	CH_2	O	4-bromophenyl	1.800	263.00	68.00	0.770	1.100
R/S	CH_2	N-$COCH_3$	CH_2	O	phenyl	0.640	113.00	—	0.110	0.050
R/S	CH_2	N-CH_3	CH_2	O	4-bromophenyl	1.400	1860.00	257.00	0.035	0.022
R/S	CH_2	N-$CONHCH_3$	CH_2	O	4-chlorophenyl	0.406	109.00	—	0.034	0.016
R/S	CH_2	S	CH_2	O	4-bromophenyl	0.333	169.00	—	0.040	—
R/S	CH_2	N-H	CH_2	O	phenyl	6.200	560.00	—	0.864	—
R/S	CH_2	S	CH_2	O	phenyl	0.647	201.00	—	0.025	0.029
R/S	CH_2	N-SO_2CH_3	CH_2	O	4-chlorophenyl	0.150	44.00	5.50	0.022	0.015

*	W	X	Y	Z	Ar	HSLN	Matr.	HFC	HG72kD	Coll3
R	CH_2	N-$CO_2C(CH_3)_3$	CH_2	O	4-chlorophenyl	0.310	142.00	—	0.007	0.006

*	W	X	Y	Z	Ar	HSLN	Matr.	HFC	HG72KD	Coll-3
S	CH_2	S	CMe_2	0	4-(furan-3-yl)phenyl	0.06	0.7	1.4	0.0017	0.002
S	CH_2	S	CMe_2	0	4(imidaz-l-yl)phnyl	0.25	5	15	0.011	0.017
R	CH_2	N-SO-(l-methyl-imidaz-l-yl)	CH_2	0	4-chlorophenyl	0.09	40	7	0.004	0.006
S	CH_2	*S=O(*R)	CH_2	0	pyrid-4-yl	1.4		32	0.094	0.13
S	CH_2	*S=O(*S)	CMe_2	0	pyrid-4-yl	2.3		31	0.49	0.16
R/S	C=O	NH	CMe_2	0	4-fluorophenyl	0.84		5.9	0.066	0.068
R/S	CH_2	CH_2	N-$COCH_3$	0	4-fluorophenyl	4.4			0.077	0.088
S	CH_2	S	CMe_2	0	4-chlorophenyl	0.059		1.3	0.017	0.001
S	CH_2	S=O	CMe_2	0	4-chlorophenyl	2.5			0.018	
S	CH_2	S	CMe_2	S	pyrid-4-yl					

*	W	X	Y	Z	Ar	HSLN	Matr.	HFC	HG72kD	Coll3
R/S	CH_2	$N\text{-}CH_3$	CH_2	O	phenyl	6.300	2177.00	—	0.101	0.158
R	CH_2	O	CH_2	O	4-chlorophenyl	0.093	77.00	8.90	0.031	0.021
R	CH_2	$N\text{-}CH_3$ (HCl salt)	CH_2	O	4-chlorophenyl	0.670	993.00	130.00	0.025	0.020
R	CH_2	N-H (HCl salt)	CH_2	O	4-chlorophenyl	1.000	171.00	34.00	0.413	0.363
R	CH_2	$N\text{-}SO_2CH_3$	CH_2	O	4-chlorophenyl	0.043	28.00	2.50	0.003	0.002
R/S	CH_2	S=O	CH_2	O	4-bromophenyl	0.410	109.00	23.00	0.013	0.017
R/S	CH_2	$N\text{-}CO_2C(CH_3)_3$	CH_2	O	4-cyanophenyl	14.000	3570.00	580.00	0.696	1.97
R/S	CH_2	$N\text{-}CO_2C(CH_3)_3$	CH_2	O	2-pyridyl	17.000	2850.00	550.00	0.716	1.640
R/S	CH_2	S	CH_2	O	4-fluorophenyl	0.530	313.00	40.00	0.028	0.035
R/S	CH_2	S=O	CH_2	O	4-fluorophenyl	0.790	306.00	28.00	0.034	0.016
R	CH_2	$N\text{-}CO_2C(CH_3)_3$	CH_2	O	4-fluorophenyl	0.490	220.00	18.00	0.026	—
R	CH_2	N-H (HCl salt)	CH_2	O	4-fluorophenyl	0.980	365.00	44.00	0.232	0.257
R	CH_2	$N\text{-}SO_2CH_3$	CH_2	O	4-fluorophenyl	0.130	52.00	4.70	0.007	0.005
R	N-H	C=O	CH_2	O	phenyl	4.600	1300.00	210.00	0.057	0.124
S	CH_2	S	CMe_2	O	4-bromophenyl	0.017	2.80	0.56	0.003	0.001
S	CH_2	S=O	CMe_2	O	4-bromophenyl	0.056	11.0	3.6	0.009	0.010
R	CH_2	$N\text{-}CH_2CO_2CH_2CH_3$ (HCl salt)	CH_2	O	4-chlorophenyl	0.250	240.00	48.00	—	—
R	CH_2	$N\text{-}SO_2CH_3$	CH_2	O	4-methoxyphenyl	0.190	74.00	16.00	—	—
R	N-H	C=O	CH_2	O	4-fluorophenyl	5.100	1840.00	187.00	0.152	—
S	CH_2	S	CMe_2	O	4-pyridyl	0.170	54.00	8.20	0.083	0.038
R	CH_2	N-H	CH_2	O	4-fluorophenyl	1.900	2060.00	176.00	0.410	0.013
S	CH_2	S	CMe_2	O	2-pyridyl	0.510	70.00	12.00	0.202	0.074

Tumor models

Primary subcutaneous tumors were established in female BDF_1 mice by trocar innoculation of the murine Lewis lung carcinoma (NIH) tumor line. This tumor line produces spontaneous lung metastases which arise from the primary tumor. Primary tumor growth was monitored by measuring the length and width of the subcutaneous tumor using calipers; lung metastases were counted at the end of the experiment (22 days after tumor implantation) by removing the lungs and counting the lesions using a dissecting microscope. The test compound was administered daily, i.p., beginning 24 hours after tumor implantation (day 1) and continuing through day 21. Primary tumor volumes and number of lung metastases were compared to control animals using an ANOVA followed by a comparison of means using the F statistic. For example, the compound of example 9(a), at a dosage of 50 mg/kg, produced a statistically significant ($p < 0.025$) tumor growth delay, calculated as the delay in reaching 1000 mm^3 tumor volume between control and treated animals, and in the number of lung metastases ($p < 0.05$) relative to the control. All drugs were administered at 50 mg/kg, i.p., daily, Day 1-Day 21. The results are presented in Table 2 below.

TABLE 2

Example No.	Tumor Growth Delay	% Inhibition-Lung Metastases
5(a)	2.0 days	13.6%
8(a)	-0.1 days	7.5%
7(a)	0.0 days	16.1%
9(a)	7.2 days ($p < 0.025$)	77.6% ($p < 0.05$)

Arthritis model

Previously frozen bovine nasal cartilage plugs weighing approximately 20 mg were embedded in polyvinyl sponges impregnated with Myobacterium tuberculosis and implanted subcutaneously in female Lewis rats. Dosing was begun 9 days after implantation and the plugs were harvested about one week later. The plugs were weighed and then

hydrolyzed and the hydroxyproline content measured. Efficaciousness was determined by the comparison of the compound-treated groups with vehicle-treated controls. The results are presented in Table 3.

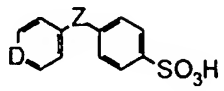
TABLE 3

Example No.	dose p.o. (mg/kg/day)	weight loss % inhibition	hydroxyproline % protection
3(a)	25	97.5	n.d.
2(b)	25	81.1	n.d.
5(a)	10	59.6	72.5
7(a)	10	77.4	86.7

$p < 0.01$ for all entries; n.d. = not determined

We claim:

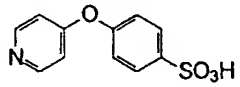
1. A compound of formula 3:



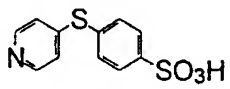
(3)

wherein D is N or C-R_{16}, wherein R_{16} is a heteroaryl group, and Z is O or S, or a salt or solvate thereof.

2. A compound according to claim 1, wherein said compound is a compound of formula 3a or 3b:



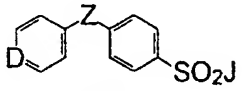
(3a)



(3b)

or a salt or solvate thereof.

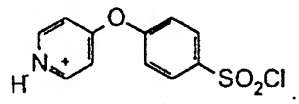
3. A compound of formula 4:



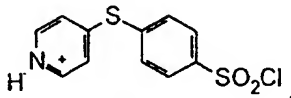
(4)

wherein D is N or C-R_{16}, wherein R_{16} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, Z is O or S, and J is a halo group, 1,2,4-triazolyl, benzotriazolyl or imidazol-1-yl, or a salt or solvate thereof.

4. A salt according to claim 3, wherein said salt is a salt of formula 4a or 4b:

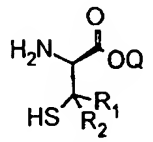


Cl^- (4a)



Cl^- (4b)

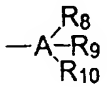
5. A compound of formula 6:



(6)

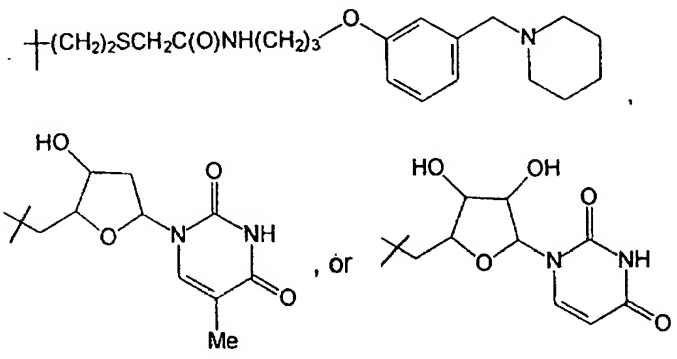
wherein R_1 and R_2 are each a methyl group, and

wherein Q is a cycloalkyl group, an aryl group, a heteroaryl group, a heterocycloalkyl group, or a group of formula



wherein A is C or Si, and R_8, R_9, and R_{10} are independently selected from H and any suitable organic moieity, or a salt or solvate thereof,

with the proviso that the compound, salt or solvate of formula 6 is not a diester and with the proviso that Q is not methyl, ethyl, isopropyl, n-butyl, -CH_2-phenyl,



6. A compound according to claim 5, wherein

when A is C,

R_8 is H, an alkyl group, an O-alkyl group, an S-alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group,

C≡N, or $C(O)R_{11}$, wherein R_{11} is an alkyl group, an aryl group, a cycloalkyl group, a heteroaryl group, or a heterocycloalkyl group, and

R_9 and R_{10} are independently selected from H, an alkyl group and an aryl group;

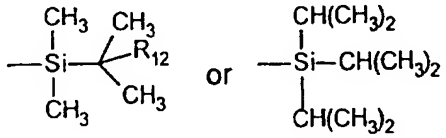
and further wherein

when A is Si,

R_8, R_9 and R_{10} are independently selected from an alkyl group, a cycloalkyl group, and an aryl group,

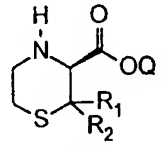
or a salt or solvate thereof.

7. A compound according to claim 6, wherein Q is $C(CH_3)_3$, CH_2-CH=CH_2, CH_2C≡N, or a group of the formula:



wherein R_{12} is CH_3 or $CH(CH_3)_2$, or a salt or solvate thereof.

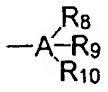
8. A compound of formula 7:



(7)

wherein R_1 and R_2 independently are selected from H and any suitable organic moiety, or where R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group, and

wherein Q is a cycloalkyl group, an aryl group, a heteroaryl group, a heterocycloalkyl group, or a group of formula



wherein A is C or Si, and R_8, R_9, and R_{10} are independently selected from H and any suitable organic moieity, or a salt or solvate thereof.

9. A compound according to claim 8, wherein R_1 and R_2 are each a methyl group, or a salt or solvate thereof.

10. A compound according to claim 9, wherein

when A is C,

R_8 is H, an alkyl group, an O-alkyl group, an S-alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, C≡N, or $C(O)R_{11}$, wherein R_{11} is an alkyl group, an aryl group, a cycloalkyl group, a heteroaryl group, or a heterocycloalkyl group, and

R_9 and R_{10} are independently selected from H, an alkyl group and an aryl group;

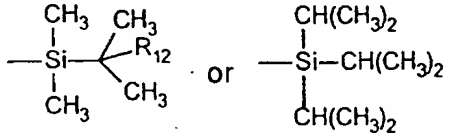
and further wherein

when A is Si,

R_8, R_9 and R_{10} are independently selected from an alkyl group, a cycloalkyl group, and an aryl group,

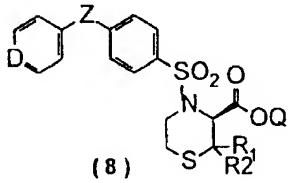
or a salt or solvate thereof.

11. A compound according to claim 10, wherein Q is CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2-CH=CH_2, $CH_2C{\equiv}N$, or a group of the formula:



wherein R_{12} is CH_3 or $CH(CH_3)_2$, or a salt or solvate thereof.

12. A compound of formula 8:



(8)

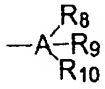
wherein

D is N

Z is O or S, and

R_1 and R_2 independently are selected from H and any suitable organic moiety, or where R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group,

and further wherein Q is a cycloalkyl group, an aryl group, a heteroaryl group, a heterocycloalkyl group, or a group of formula



wherein A is C or Si, and R_8, R_9, and R_{10} are independently selected from H and any suitable organic moieity, or a salt or solvate thereof.

13. A compound according to claim 12, wherein R_1 and R_2 are each a methyl group, or a salt or solvate thereof.

14. A compound according to claim 13, wherein

when A is C,

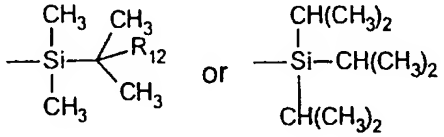
R_8 is H, an alkyl group, an O-alkyl group, an S-alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, C≡N, or $C(O)R_{11}$, wherein R_{11} is an alkyl group, an aryl group, a cycloalkyl group, a heteroaryl group, or a heterocycloalkyl group, and

R_9 and R_{10} are independently selected from H, an alkyl group and an aryl group; and

when A is Si, R_8, R_9 and R_{10} are independently selected from an alkyl group, a cycloalkyl group, and an aryl group,

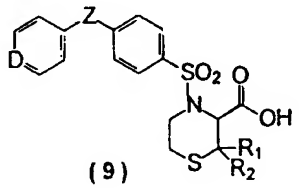
or a salt or solvate thereof.

15. A compound according to claim 14, wherein Q is CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2-CH=CH_2, $CH_2C{\equiv}N$, or a group of the formula:



wherein R_{12} is CH_3 or $CH(CH_3)_2$, or a salt or solvate thereof.

16. A compound of formula 9:



(9)

wherein

D is N,

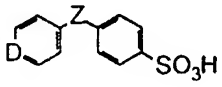
Z is O or S, and

R_1 and R_2 independently are selected from H and any suitable organic moiety, or where R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group,

or a salt or solvate thereof.

17. A compound according to claim 16 wherein R_1 and R_2 are each a methyl group, or a salt or solvate thereof.

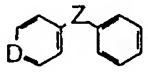
18. A method of making a compound of formula 3:



(3)

wherein D is N or C-R_{16}, wherein R_{16} is a heteroaryl group, and Z is O or S, or a salt or solvate thereof,

comprising the step of converting a compound of formula 2:

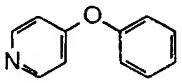


(2)

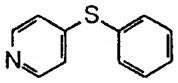
wherein D and Z are as defined above, or a salt or solvate thereof,

to a compound of formula 3, or a salt or solvate thereof, under conditions sufficient to form said compound of formula 3.

19. A method according to claim 18, comprising the step of converting a compound of formula 2a or 2b:



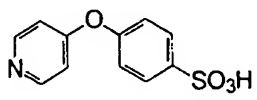
(2a)



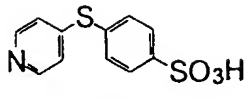
(2b)

or a salt or solvate thereof,

to a compound of formula 3a or 3b:



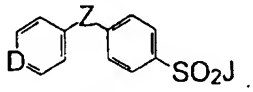
(3a)



(3b)

or a salt or solvate thereof, under conditions sufficient to form said compound of formula 3a or 3b, or a salt or solvate thereof.

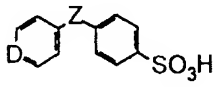
20. A method of making a compound of formula 4:



(4)

wherein D is N or C-R_{16}, wherein R_{16} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, Z is O or S, and J is a halogen, 1,2,4-triazolyl, benzotriazolyl or imidazol-1-yl, or a salt or solvate thereof,

comprising the step of converting a compound of formula 3:

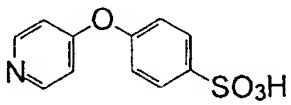


(3)

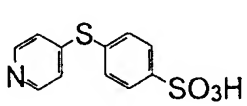
wherein D and Z are as defined above, or a salt or solvate thereof,

to a compound of formula 4, or a salt or solvate thereof, under conditions sufficient to form a compound of formula 4, or a salt or solvate thereof.

21. A method according to claim 20, comprising the step of converting a compound of formula 3a or 3b:



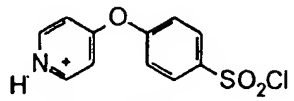
(3a)



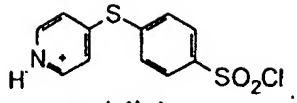
(3b)

or a salt or solvate thereof,

to a salt of formula 4a or 4b:



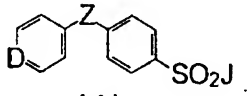
Cl⁻ (4a)



Cl (4b)

or a solvate thereof, under conditions sufficient to form said compound of formula 4a or 4b, or a salt or solvate thereof.

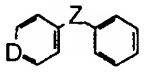
22. A method of making a compound of formula 4:



(4)

wherein D is N or C-R_{16}, wherein R_{16} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, Z is O or S, and J is a halogen, 1,2,4-triazolyl, benzotriazolyl or imidazol-1-yl, or a salt or solvate thereof,

comprising the step of converting a compound of formula 2:

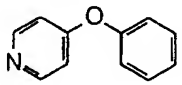


(2)

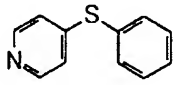
wherein D and Z are as defined above, or a salt or solvate thereof,

to a compound of formula 4, or a salt or solvate thereof, under conditions sufficient to form a compound of formula 4, or a salt or solvate thereof.

23. A method according to claim 22, comprising the step of converting a compound of formula 2a or 2b:



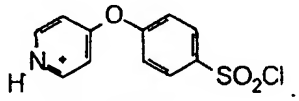
(2a)



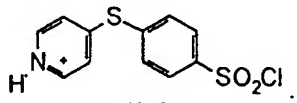
(2b)

or a salt or solvate thereof,

to a salt of formula 4a or 4b:



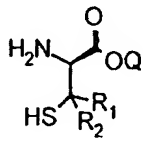
(4a)



(4b)

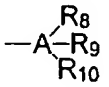
or a solvate thereof, under conditions sufficient to form said compound of formula 4a or 4b, or a solvate thereof.

24. A method of making a compound of formula 6:

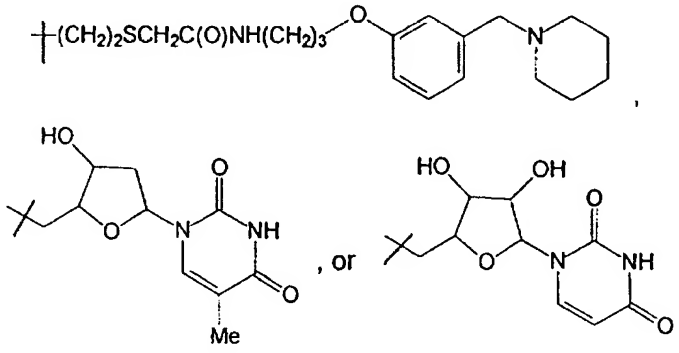


(6)

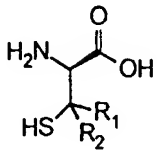
wherein R_1 and R_2 are each a methyl group, and
wherein Q is a cycloalkyl group, an aryl group, a heteroaryl group, a heterocycloalkyl group, or a group of formula



wherein A is C or Si, and R_8, R_9, and R_{10} are independently selected from H and any suitable organic moiety, or a salt or solvate thereof,
with the proviso that the compound, salt or solvate of formula 6 is not a diester and with the proviso that A is not methyl, ethyl, isopropyl, n-butyl, -CH_2-phenyl,



comprising the step of converting a compound of formula 5:



(5)

wherein R_1 and R_2 are as defined above, or a salt or solvate thereof, to a compound of formula 6, or a salt or solvate thereof, under conditions sufficient to form said compound of formula 6, or a salt or solvate thereof.

25. A method according to claim 24, wherein

when A is C,

R_8 is H, an alkyl group, an O-alkyl group, an S-alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, C≡N, or $C(O)R_{11}$, wherein R_{11} is an alkyl group, an aryl group, a cycloalkyl group, a heteroaryl group, or a heterocycloalkyl group, and

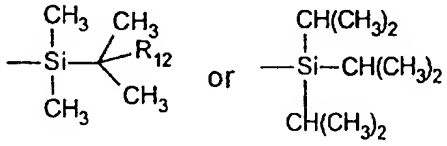
R_9 and R_{10} are independently selected from H, an alkyl group and an aryl group, with the proviso that R_9 and R_{10} are not both methyl groups;

and further wherein

when A is Si,

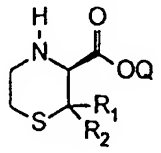
R_8, R_9 and R_{10} are independently selected from an alkyl group, a cycloalkyl group, and an aryl group.

26. A method according to claim 25, wherein Q is $C(CH_3)_3$, CH_2-$CH=CH_2$, $CH_2C\equiv N$, or a group of the formula:



wherein R_{12} is CH_3 or $CH(CH_3)_2$, or a salt or solvate thereof.

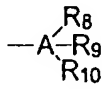
27. A method of making a compound of formula 7:



(7)

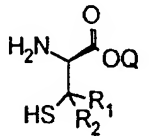
wherein R_1 and R_2 independently are selected from H and any suitable organic moiety, or where R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group, and

wherein Q is a cycloalkyl group, an aryl group, a heteroaryl group, a heterocycloalkyl group, or a group of formula



wherein A is C or Si, and R_8, R_9, and R_{10} are independently selected from H and any suitable organic moieity, or a salt or solvate thereof,

comprising the step of converting a compound of formula 6:



(6)

wherein R_1, R_2 and Q are as defined above, or a salt or solvate thereof, to a compound of formula 7, or a salt or solvate thereof, under conditions sufficient to form said compound of formula 7, or a salt or solvate thereof.

28. A method according to claim 27, wherein R_1 and R_2 are each a methyl group.

29. A method according to claim 28, wherein

when A is C,

R_8 is H, an alkyl group, an O-alkyl group, an S-alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group,

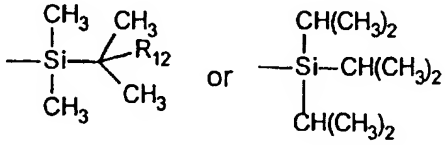
C≡N, or $C(O)R_{11}$, wherein R_{11} is an alkyl group, an aryl group, a cycloalkyl group, a heteroaryl group, or a heterocycloalkyl group, and

R_9 and R_{10} are independently selected from H, an alkyl group and an aryl group;

and further wherein

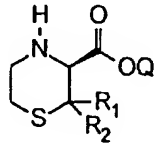
when A is Si, R_8, R_9 and R_{10} are independently selected from an alkyl group, a cycloalkyl group, and an aryl group.

30. A method according to claim 29, wherein Q is CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2-CH=CH_2, $CH_2C{\equiv}N$, or a group of the formula:



wherein R_{12} is CH_3 or $CH(CH_3)_2$.

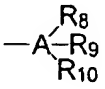
31. A method of making a compound of formula 7:



(7)

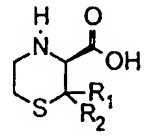
wherein R_1 and R_2 independently are selected from H and any suitable organic moiety, or where R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group, and

wherein Q is a cycloalkyl group, an aryl group, a heteroaryl group, a heterocycloalkyl group, or a group of formula



wherein A is C or Si, and R_8, R_9, and R_{10} are independently selected from H or any suitable organic moieity, or a salt or solvate thereof,

comprising the step of converting a compound of formula 11:



(11)

wherein R_1 and R_2 are as defined above, or a salt or solvate thereof, to a compound of formula 7, or a salt or solvate thereof, under conditions sufficient to form said compound of formula 7, or a salt or solvate thereof.

32. A method according to claim 31, wherein R_1 and R_2 are each a methyl group.

33. A method according to claim 32, wherein

when A is C,

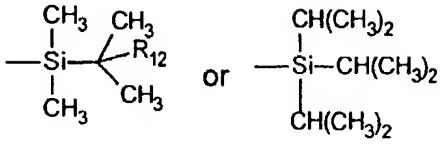
R_8 is H, an alkyl group, an O-alkyl group, an S-alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, C≡N, or $C(O)R_{11}$, wherein R_{11} is an alkyl group, an aryl group, a cycloalkyl group, a heteroaryl group, or a heterocycloalkyl group, and

R_9 and R_{10} are independently selected from H, an alkyl group and an aryl group;

and further wherein

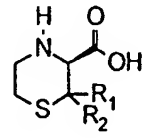
when A is Si, R_8, R_9 and R_{10} are independently selected from an alkyl group, a cycloalkyl group, and an aryl group.

34. A method according to claim 33, wherein Q is CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2-CH=CH_2, $CH_2C{\equiv}N$, or a group of the formula:



wherein R_{12} is CH_3 or $CH(CH_3)_2$.

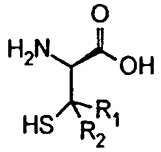
35. A method of making a compound of formula 11:



(11)

wherein R_1 and R_2 independently are a methyl group, or a salt or solvate thereof,

comprising the step of converting a compound of formula 5:

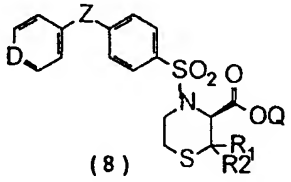


(5)

wherein R_1 and R_2 are as defined above, or a salt or solvate thereof,

to a compound of formula 11, or a salt or solvate thereof.

36. A method of making a compound of formula 8:



(8)

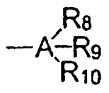
wherein

D is N or C-R_{16}, wherein R_{16} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group,

Z is O or S, and

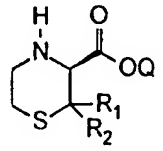
R_1 and R_2 independently are selected from H and any suitable organic moiety, or where R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group,

and further wherein Q is a cycloalkyl group, an aryl group, a heteroaryl group, a heterocycloalkyl group, or a group of formula



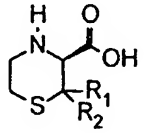
wherein A is C or Si, and R_8, R_9, and R_{10} are independently H or any suitable organic moieity, or a salt or solvate thereof,

comprising the step of reacting a compound of formula 7 or formula 11:



(7)

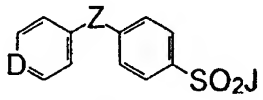
wherein R_1, R_2



(11)

and Q are as defined above, or a salt or solvate thereof,

with a compound of formula 4:



(4)

wherein D and Z are as defined above, and J is a halogen, 1,2,4-triazolyl, benzotriazolyl or imidazol-1-yl, or a salt or solvate thereof,

under conditions sufficient to form said compound of formula 8, or a salt or solvate thereof.

37. A method according to claim 36, wherein R_1 and R_2 are each a methyl group.

38. A method according to claim 37, wherein

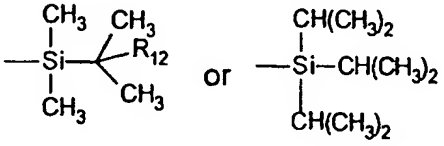
when A is C,

R_8 is H, an alkyl group, an O-alkyl group, an S-alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, C≡N, or $C(O)R_{11}$, wherein R_{11} is an alkyl group, an aryl group, a cycloalkyl group, a heteroaryl group, or a heterocycloalkyl group, and

R_9 and R_{10} are independently selected from H, an alkyl group and an aryl group; and

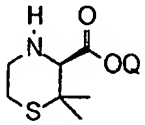
when A is Si, R_8, R_9 and R_{10} are independently selected from an alkyl group, a cycloalkyl group, and an aryl group.

39. A method according to claim 38, wherein Q is CH_3, CH_2CH_3, $CH(CH_3)_3$, $C(CH_3)_3$, CH_2-CH=CH_2, $CH_2C{\equiv}N$, or a group of the formula:



wherein R_{12} is CH_3 or $CH(CH_3)_2$.

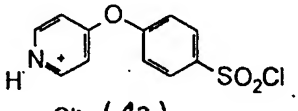
40. A method according to claim 36, comprising the step of reacting a compound of formula 7a:



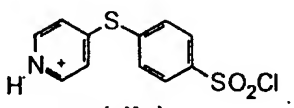
(7a)

or a salt or solvate thereof,

with a salt of formula 4a or 4b:



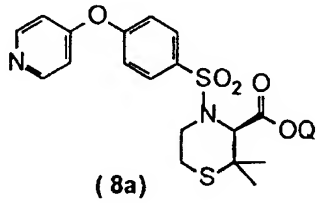
Cl^- (4a)



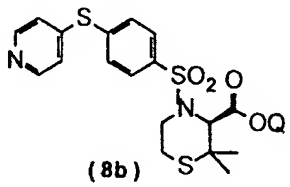
Cl (4b)

or a solvate thereof,

under conditions sufficient to form a compound of formula 8a or 8b:



(8a)



(8b)

or a salt or solvate thereof.

41. A method according to claim 40, wherein

when A is C,

R_8 is H, an alkyl group, an O-alkyl group, an S-alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, $C{\equiv}N$, or $C(O)R_{11}$, wherein R_{11} is an alkyl group, an aryl group, a cycloalkyl group, a heteroaryl group, or a heterocycloalkyl group, and

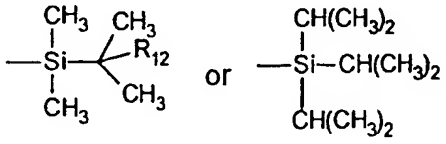
R_9 and R_{10} are independently selected from H, an alkyl group and an aryl group;

and further wherein

when A is Si,

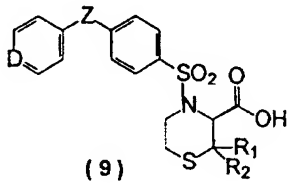
R_8, R_9 and R_{10} are independently selected from an alkyl group, a cycloalkyl group, and an aryl group.

42. A method according to claim 41, wherein Q is CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2-CH=CH_2, $CH_2C{\equiv}N$, or a group of the formula:



wherein R_{12} is CH_3 or $CH(CH_3)_2$.

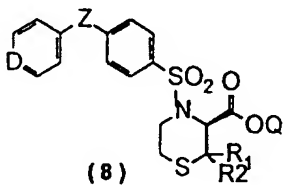
43. A method of making a compound of formula 9:



(9)

wherein D is N, Z is O or S, and R_1 and R_2 independently are selected from H and any suitable organic moiety or R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group, or a salt or solvate thereof,

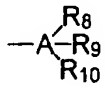
comprising the step of converting a compound of formula 8:



(8)

wherein D, Z, R_1, and R_2 are as defined above, and

further wherein Q is a cycloalkyl group, an aryl group, a heteroaryl group, a heterocycloalkyl group, or a group of formula



wherein A is C or Si, and R_8, R_9, and R_{10} are independently selected from H and any suitable organic moieity, or a salt or solvate thereof,

to a compound of formula 9, or a salt or solvate thereof, under conditions sufficient to form said compound of formula 9, or a salt or solvate thereof.

44. A method according to claim 43, wherein R_1 and R_2 are each a methyl group.

45. A method according to claim 44, wherein

when A is C,

R_8 is H, an alkyl group, an O-alkyl group, an S-alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, C≡N, or $C(O)R_{11}$, wherein R_{11} is an alkyl group, an aryl group, a cycloalkyl group, a heteroaryl group, or a heterocycloalkyl group, and

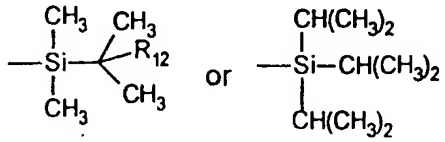
R_9 and R_{10} are independently selected from H, an alkyl group and an aryl group;

and further wherein

when A is Si,

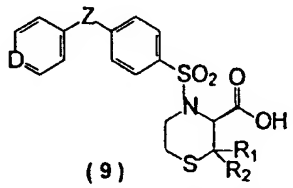
R_8, R_9 and R_{10} are independently selected from an alkyl group, a cycloalkyl group, and an aryl group.

46. A method according to claim 45, wherein Q is CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2-CH=CH_2, $CH_2C{\equiv}N$, or a group of the formula:



wherein R_{12} is CH_3 or $CH(CH_3)_2$.

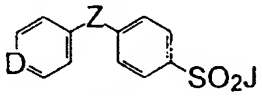
47. A method of making a compound of formula 9:



(9)

wherein D is N, Z is O or S, and R_1 and R_2 independently are selected from H and any suitable organic moiety or R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group, or a salt or solvate thereof,

comprising the step of converting a compound of formula 4:

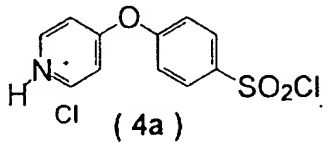


(4)

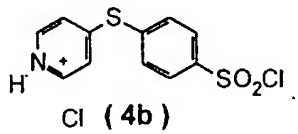
wherein D and Z are as defined above, and J is a halogen, 1,2,4-triazolyl, benzotriazolyl or imidazol-1-yl , or a salt or solvate thereof,

to a compound of formula 9, or a salt or solvate thereof, under conditions sufficient to form said compound of formula 9, or a salt or solvate thereof.

48. A method according to claim 47, wherein said salt of formula 4 is a salt of formula 4a or 4b:

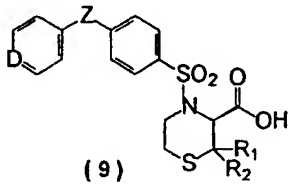


(4a)



(4b)

49. A method of making a compound of formula 9:

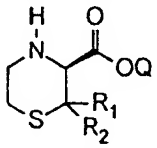


(9)

wherein D is N or C-R_{16}, wherein R_{16} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, Z is O or S, and further wherein R_1 and R_2 independently are selected from H and any suitable organic moiety, or where R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group,

or a salt or solvate thereof,

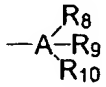
comprising the step of converting a compound of formula 7:



(7)

wherein R_1 and R_2 are as defined above, and

wherein Q is a cycloalkyl group, an aryl group, a heteroaryl group, a heterocycloalkyl group, or a group of formula



wherein A is C or Si, and R_8, R_9, and R_{10} are independently selected from H and any suitable organic moieity, or a salt or solvate thereof,

to a compound of formula 9, or a salt or solvate thereof, under conditions sufficient to form said compound of formula 9.

50. A method according to claim 49, wherein R_1 and R_2 are each a methyl group.

51. A method according to claim 50, wherein D is N.

52. A method according to claim 51, wherein

when A is C,

R_8 is H, an alkyl group, an O-alkyl group, an S-alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, C≡N, or $C(O)R_{11}$, wherein R_{11} is an alkyl group, an aryl group, a cycloalkyl group, a heteroaryl group, or a heterocycloalkyl group, and

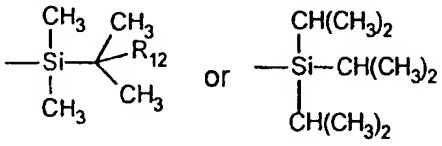
R_9 and R_{10} are independently selected from H, an alkyl group and an aryl group;

and further wherein

when A is Si,

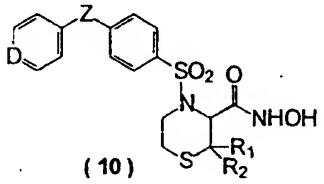
R_8, R_9 and R_{10} are independently selected from an alkyl group, a cycloalkyl group, and an aryl group.

53. A method according to claim 52, wherein Q is CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2-CH=CH_2, $CH_2C{\equiv}N$, or a group of the formula:



wherein R_{12} is CH_3 or $CH(CH_3)_2$.

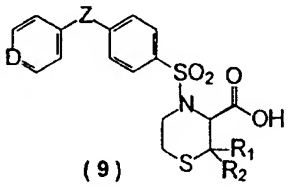
54. A method of making a compound of formula 10:



(10)

wherein D is N, Z is O or S, and R_1 and R_2 independently are selected from H and any suitable organic moiety or R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group, or a salt or solvate thereof,

comprising the step of converting a compound of formula 9:

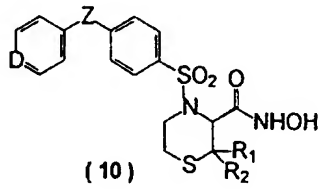


(9)

wherein D, Z, R_1, and R_2 are as defined above, or a salt or solvate thereof, to a compound of formula 10, or a salt or solvate thereof, under conditions sufficient to form said compound of formula 10, or a salt or solvate thereof.

55. A method according to claim 54, wherein R_1 and R_2 are each a methyl group.

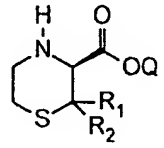
56. A method of making a compound of formula 10:



(10)

wherein D is N or C-R_{16}, wherein R_{16} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group, and further wherein R_1 and R_2 are independently selected from H and any suitable organic moiety, or where R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group, or a salt or solvate thereof,

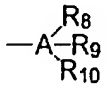
comprising the step of converting a compound of formula 7:



(7)

wherein R_1 and R_2 are as defined above, and

wherein Q is a cycloalkyl group, an aryl group, a heteroaryl group, a heterocycloalkyl group, or a group of formula



wherein A is C or Si, and R_8, R_9, and R_{10} are independently selected from H and any suitable organic moieity, or a salt or solvate thereof

to a compound of formula 10, or a salt or solvate thereof, under conditions sufficient to form said compound of formula 10, or a salt or solvate thereof.

57. A method according to claim 56, wherein R_1 and R_2 are each a methyl group.

58. A method according to claim 57, wherein D is N.

59. A method according to claim 58, wherein

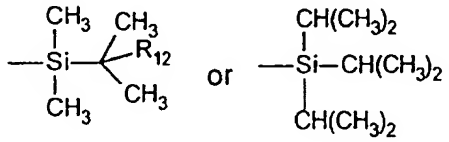
when A is C,

R_8 is H, an alkyl group, an O-alkyl group, an S-alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, C≡N, or $C(O)R_{11}$, wherein R_{11} is an alkyl group, an aryl group, a cycloalkyl group, a heteroaryl group, or a heterocycloalkyl group, and

R_9 and R_{10} are independently selected from H, an alkyl group and an aryl group; and

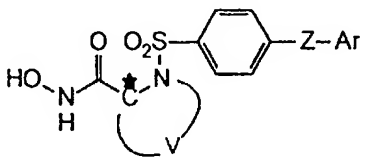
when A is Si, R_8, R_9 and R_{10} are independently selected from an alkyl group, a cycloalkyl group, and an aryl group.

60. A compound according to claim 59, wherein Q is CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2-CH=CH_2, $CH_2C{\equiv}N$, or a group of the formula:



wherein R_{12} is CH_3 or $CH(CH_3)_2$.

61. A compound of formula 1:



wherein:

Z is O or S;

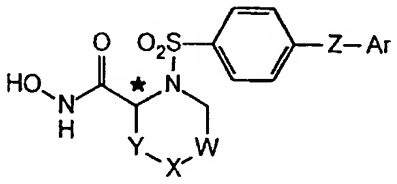
V is a divalent radical which together with C* and N forms a ring having six ring atoms, where each of said ring atoms other than C* and N independently is unsubstituted or substituted by a suitable substituent, and at

least one of said other ring atoms is a heteroatom selected from O, N and S, and the remainder are carbon atoms; and

Ar is an aryl or heteroaryl group;

or a pharmaceutically acceptable prodrug, salt or solvate thereof.

62. A compound according to claim 61, wherein said compound has the formula 1-a:



wherein:

W, X and Y are each, independently of one another, CR_1R_2, C=O,

S, S=O, SO_2, O, N-R_3, or $N^+(O^-)$-R_4, where

R_1 and R_2 are independently selected from H and a suitable organic moiety, or wherein R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group,

R_3 is hydrogen or a suitable organic moiety, and

R_4 is an alkyl group,

with the proviso that at least one, but not all, of W, X, and Y are selected from CR_1R_2 and C=O,

or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

63. A compound according to claim 62, wherein R_1 and R_2 are independently selected from H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, OR_5, SR_5, NR_5R_6, and $C(O)R_7$, where

R_5 is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, or $C(O)NR_{13}R_{14}$,

where R_{13} and R_{14} are independently selected from H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, and a heteroaryl group, or R_{13} and R_{14},

together with the nitrogen atom to which they are attached form a heterocycloalkyl group,

R_6 is H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, C(O)O-R_{15}, C(O)S-R_{15}, or SO_2-R_{15},

wherein R_{15} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group,

R_7 is OH, an alkyl group, a cycloalkyl group, a heterocyclolalkyl group, an aryl group, a heteroaryl group, an O-alkyl group, $NR_{13}R_{14}$, or O-R_{15}, wherein R_{13}, R_{14}, and R_{15} are independently as defined above,

or wherein R_1 and R_2 together form a cycloalkyl group or a heterocycloalkyl group,

or a pharmaceutically acceptable prodrug, salt or solvate thereof.

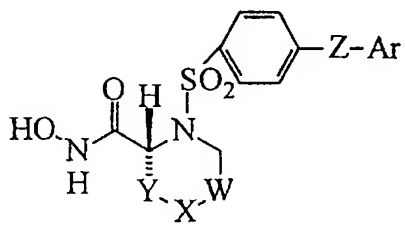
64. A compound according to claim 62, where R_3 is hydrogen, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, C(O)-$NR_{13}R_{14}$, C(O)-OR_{15}, C(O)-SR_{15}, SO_2-R_{15}, or C(O)-R_{13}

where R_{13} and R_{14} are independently selected from H, an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, and a heteroaryl group, or R_{13} and R_{14}, together with the nitrogen atom to which they are attached form a heterocycloalkyl group,and

R_{15} is an alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group,

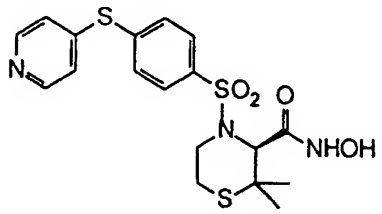
or a pharmaceutically acceptable prodrug, salt or solvate thereof.

65. A compound according to claim 62, wherien said compound has the formula:



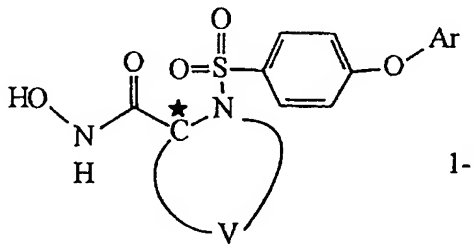
or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

66. A compound according to claim 62, wherein said compound has the formula:



or a pharmaceutically acceptable prodrug, salt or solvate thereof.

67. A compound of the formula 1-f:



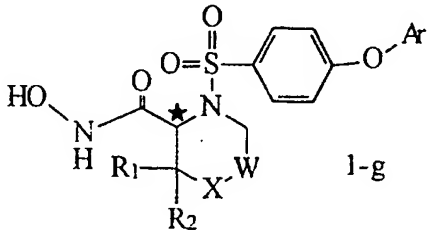
1-f

wherein:

V is a divalent radical which together with C* and N forms a ring having six ring atoms, where each of said ring atoms other than C* and N independently is unsubstituted or substituted by a suitable substituent, and at least one of said other ring atoms is a heteroatom selected from O, N and S, and the remainder are carbon atoms; and

Ar is a monocyclic aryl group or monocyclic heteroaryl group; or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

68. A compound as claimed in claim 67 having the formula 1-g



1-g

wherein:

W and X are independently selected from CH_2, C=O, S, S=O, O, N-R_3, and $N^+(O^-)$-R_4, where

R_3 is a hydrogen atom or a suitable substituent, and

R_4 is a C_1-C_7 alkyl group, wherein said alkyl group is a straight or branched chain monovalent radical of carbon and hydrogen atoms having no unsaturation, which is optionally substituted by one or more suitable substituents,

provided that when W is CH_2 or C=O, X is not CH_2 or C=O; and

R_1 and R_2 are independently selected from a hydrogen atom, a C_1-C_7 alkyl group, a -C(O)OR_{17} group, or a -C(O)$NR_{17}R_{18}$ group,

wherein R_{17} is hydrogen or an alkyl group, and R_{18} is an alkyl group,

and wherein each of said alkyl groups is a straight or branched chain monovalent radical of carbon and hydrogen atoms having no unsaturation, which is optionally substituted by one or more suitable substituents;

or R_1 and R_2 together form a monocyclic cycloalkyl group or a monocyclic heterocycloalkyl group,

or a pharmaceutically acceptable prodrug thereof or a pharmaceutically acceptable salt thereof.

69. A compound as claimed in claim 68 wherein W is CH_2 and

X is S, S=O, O, N-R_3 or $N^+(O^-)$-R_4; or a pharmaceutically acceptable prodrug thereof or a pharmaceutically acceptable salt thereof.

70. A compound as claimed in claim 69 wherein R_3 is a hydrogen atom, an alkyl group, wherein said alkyl group is a straight or branched chain monovalent radical of carbon and hydrogen atoms having no unsaturation, which is optionally substituted by one or more suitable substituents, a C(O)-R_{17} group, a C(O)O-R_{17} group, a C(O)NH-R_{17} group, a

$C(O)NR_{17}R_{18}$ group, an SO_2-R_{19} group, wherein R_{17} and R_{18} are each independently an alkyl group wherein said alkyl group is a straight or branched chain monovalent radical of carbon and hydrogen atoms having no unsaturation, which is optionally substituted by one or more suitable substituents, and wherein R_{19} is a monocyclic aryl group or an alkyl group as defined above; or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

71. A compound as claimed in claim 68, wherein W is S, O or N-R_3 and X is CH_2; or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

72. A compound as claimed in claim 68, wherein W is N-R_3 and X is C=O; or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

73. A compound as claimed in claim 68, wherein W is C=O and X is S, O or N-R_3; or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

74. A compound as claimed in claim 68 wherein Ar is a monocyclic aryl group which is unsubstituted or substituted in the para position with a suitable substituent; or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

75. A compound as claimed in claim 74 wherein said suitable substituent in the para position of said aryl group is a halogen atom, an O-alkyl group, wherein said alkyl group is a straight or branched chain monovalent radical of carbon and hydrogen atoms having no unsaturation, which is optionally substituted by one or more suitable substituents, or a monocyclic heteroaryl group; or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

76. A compound as claimed in claim 68 wherein the carbon atom designated with "*" is in the R-configuration when X is CH_2, C=O, O, N-R_3 or $N^+(O^-)R_4$ and in the S-configuration when X is S or S=O; or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

77. A compound as claimed in claim 75 wherein said suitable substituent in the para position of said aryl group is fluorine, chlorine, a methoxy group, or an imidazolyl group; or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

78. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of a compound as defined in claim 61 or a pharmaceutically acceptable prodrug, salt or solvate thereof; and

(b) a pharmaceutically acceptable carrier, diluent, vehicle or excipient.

79. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of a compound as defined in claim 67 or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier, diluent, vehicle or excipient.

80. A method of treating a mammalian disease condition mediated by metalloproteinase activity which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound as defined in claim 61 or a pharmaceutically acceptable prodrug, salt or solvate thereof.

81. A method of treating a mammalian disease condition mediated by metalloproteinase activity which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound as defined in claim 67 or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

82. A method according to claim 80 wherein the mammalian disease condition is tumor growth, invasion or metastasis, or arthritis.

83. A method according to claim 81 wherein the mammalian disease condition is tumor growth, invasion or metastasis, or arthritis.

84. A method of inhibiting the activity of a metalloproteinase which comprises contacting the metalloproteinase with an effective amount of

a compound as defined in claim 61 or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

85. A method of inhibiting the activity of a metalloproteinase which comprises contacting the metalloproteinase with an effective amount of a compound as defined in claim 67 or a pharmaceutically acceptable prodrug or a pharmaceutically acceptable salt thereof.

86. A compound according to claim 61 selected from 2(R)-N-hydroxy-1-(4-(4-chlorophenoxy)benzenesulfonyl)-4-(methanesulfonyl)-piperazine-2-carboxamide; 2(R)-N-hydroxy-1-(4-(4-fluorophenoxy)benzenesulfonyl)-4-(methanesulfonyl)-piperazine-2-carboxamide; and 3(S)-N-hydroxy-4-(4-((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide; and pharmaceutically acceptable salts and pharmaceutically acceptable prodrugs thereof.

87. A compound according to claim 86 which is 3(S)-N-hydroxy 4-(4-((pyrid-4-yl)oxy)benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide; or a pharmaceutically acceptable salt or a pharmaceutically acceptable prodrug thereof.

88. A compound according to claim 67 wherein no more than two of said four ring atoms of V are a heteroatom independently selected from O, N and S.

89. A compound according to claim 61, wherein said compound is selected from:

3(S)-N-hydroxy-4-(4-(4-imidazol-1-yl)phenoxy)benzenesulfonyl-2,2-dimethyl-tetrahydro-2H-thiazine-3-carboxamide,

3(S)-N-hydroxy-4-(4-(4-flourophenoxy)benzenesulfonyl-2,2-dimethyl-tetrahydro-2H-thiazine-3-carboxamide,

3(S)-N-hydroxy-4-(4-(4-imidazol-2-yl)phenoxy)benzenesulfonyl-2,2-dimethyl-tetrahydro-2H-thiazine-3-carboxamide,

3(S)-N-hydroxy-4-(4-(4-chlorophenoxy)benzenesulfonyl-2,2-dimethyl-tetrahydro-2H-thiazine-3-carboxamide,

2(R)-3,3-Dimethyl-N-hydroxy-1-(4-(4-chlorophenoxyl)benzenesulfonyl)-piperazine-2-carboxamide,

2(R)-3,3-Dimethyl-N-hydroxy-1-(4-(4-fluorophenoxyl)benzenesulfonyl)-piperazine-2-carboxamide,

2(R)-3,3-Dimethyl-N-hydroxy-1-(4-(4-bromophenoxyl)benzenesulfonyl)-piperazine-2-carboxamide,

2(R)-1-(4-(4-(Chlorophenoxybenzenesulfonyl)-N-hydroxy-3,3,4-trimethylpiperazine-2-carboxamide,

2(R)-1-(4-(4-(Fluorophenoxybenzenesulfonyl)-N-hydroxy-3,3,4-trimethylpiperazine-2-carboxamide,

3(S)-N-hydroxy-4-(4-(4-chlorophenylsulfanyl)benzenesulfonyl-2,2-dimethyl-tetrahydro-2H-thiazine-3-carboxamide,

3(S)-N-hydroxy-4-(4-(4-fluorophenylsulfanyl)benzenesulfonyl-2,2-dimethyl-tetrahydro-2H-thiazine-3-carboxamide,

2(R)-3,3-Dimethyl-N-hydroxy-1-(4-(4-fluorophenylsulfanyl)benzenesulfonyl)-piperazine-2-carboxamide,

2(R)-3,3-Dimethyl-N-hydroxy-1-(4-(4-chlorophenylsulfanyl)benzenesulfonyl)-piperazine-2-carboxamide,

2(R)-1-(4-(4-(Fluorophenylsulfanyl)benzenesulfonyl)-N-hydroxy-3,3,4-trimethylpiperazine-2-carboxamide,

2(R)-1-(4-(4-(Chlorophenylsulfanyl)benzenesulfonyl)-N-hydroxy-3,3,4-trimethylpiperazine-2-carboxamide,

2(R),3(S)-N-hydroxy-4-(4-(pyrid-4-yl)oxy)benzenesulfonyl)-2-methyl-tetrahydro-2H-thiazine-3-carboxamide, and

2(R),3(S)-N-hydroxy-4-(4-(pyrid-4-yl)sulfanyl)benzenesulfonyl)-2-methyl-tetrahydro-2H-thiazine-3-carboxamide;

or a pharmaceutically acceptable prodrug, salt, or solvate thereof.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/19328

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D241/04 C07D401/12 C07D279/12 C07D265/30 C07D417/12
A61K31/44 A61K31/50 A61K31/54 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 96 33172 A (PFIZER ;PISCOPIO ANTHONY D (US); RIZZI JAMES P (US)) 24 October 1996 see the whole document ---	1-89
A,P	WO 96 00214 A (CIBA GEIGY AG ;MACPHERSON LAWRENCE JOSEPH (US); PARKER DAVID THOMA) 4 January 1996 cited in the application see the whole document ---	61,78-85
A	WO 94 24140 A (BRITISH BIO TECHNOLOGY ;CRIMMIN MICHAEL JOHN (GB); AYSCOUGH ANDREW) 27 October 1994 cited in the application see the whole document --- -/--	1-89

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 1997	21.04.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/19328

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TETRAHEDRON LETTERS, vol. 25, no. 37, 1984, OXFORD GB, pages 4157-4160, XP002029636 N.K. CAPPS ET AL.: "Novel catalytic rearrangements of 2-vinyl-1,3-thiazetidines" see page 4158	5,6
X	JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, no. 7, 1993, LETCHWORTH GB, pages 641-642, XP002029637 S. CUMBERBATCH ET AL.: "The synthesis and conformational analysis of a pair of diastereoisomeric cyclic peptides with cis and trans amide bonds, respectively" see scheme 1	5,6
X	JOURNAL OF ORGANIC CHEMISTRY, vol. 27, 1962, EASTON US, pages 4227-4231, XP002029638 G.N. WALKER: "Vinylogous amides of 2-methylaminoethanol and their behavior with lithium aluminium hydride. Vinylogous urethanes of ethanolamines and their acetylation." see page 4231	5,6
X	JOURNAL OF ORGANIC CHEMISTRY, vol. 39, no. 4, 1974, EASTON US, pages 437-440, XP002029639 R.A. FIRESTONE ET AL.: "Total synthesis of beta-lactam antibiotics. IV. Epimerization of 6(7)-aminopenicillins and -cephalosporins from alpha to beta1." see compound 13	5,6
X	CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 29, no. 6, 1981, TOKYO JP, pages 1554-1560, XP002029640 K. SAKAI ET AL.: "Convenient synthesis of 1,4-thiazine-3-carboxylic acid derivatives" see compound 9	8

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 96/ 19328

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 80-85
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/US 96/19328

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9633172 A	24-10-96	AU 5080296 A	31-10-96
		CN 1140165 A	15-01-97
		CZ 9601130 A	13-11-96
		NO 961585 A	21-10-96
WO 9600214 A	04-01-96	US 5506242 A	09-04-96
		AU 2536995 A	19-01-96
		CA 2192092 A	04-01-96
		EP 0766672 A	09-04-97
		FI 965156 A	20-12-96
		US 5552419 A	03-09-96
		ZA 9505206 A	27-12-95
WO 9424140 A	27-10-94	AU 6510294 A	08-11-94
		DE 69401926 D	10-04-97
		EP 0694036 A	31-01-96